Induced Hibernation by α2-Adrenoceptor Agonists[a]

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Guanabenz, 2,6-dichlorobenzylidene aminoguanidine, is an α2-adrenoceptor agonist and is considered to act similarly to clonidine with respect to side effects and efficacy.[1,2] Three adrenoceptor agonists—two commonly employed anesthetic agents and a minor tranquilizer—were compared in the rat for their effect on core temperature and behavior. At an ambient temperature of 26.7 °C, 24 Sprague-Dawley rats were injected intraperitoneally (i.p.) with guanabenz acetate (12 mg/kg), clonidine (0.3 mg/kg), pentobarbital (35 mg/kg), ketamine HCl (35 mg/kg), diazepam (6 mg/kg), guanabenz + diazepam, and guanabenz + pentobarbital at the same stated doses. Within 45 min, the mean core temperature of the animals dropped to 27.5, 34.5, 33.6, 35.1, 37.6, 30.7, and 29.3 °C, respectively. The patellar, urethroanal (bulbocavernosus), startle, and corneal reflexes were absent after 30 min in guanabenz, pentobarbital, ketamine, guanabenz plus pentobarbital treated animals, but they were present in clonidine and diazepam treated animals. In the rats treated with a combination of the drugs guanabenz and diazepam, the urethroanal and vestibular reflexes were absent. Other reflexes, that is, withdrawal, tail compression response, corneal, and righting were present in these animals. Those rats receiving clonidine showed signs of sedation but not anesthesia. Guanabenz (12 mg/kg) was administered i.p. to eight Sprague-Dawley rats. Immediately after injection of guanabenz or the vehicle (5% aqueous dextrose) into another group of eight animals, the rats were placed in a temperature-controlled room (4–5 °C). The brain temperature of the control rats did not drop appreciably. By comparison, the brain temperature of the guanabenz-treated rats dropped by 10 °C (from 37 °C to 27 °C) whereas colonic temperature dropped from 37 °C to 17 °C, representing a fall of 20 °C in core temperature (FIG. 1). Three sets of two rats each were kept in the state of hibernation for 3, 7, and 12 days, with repeated injections, without any untoward effect. One of the rats carried for 12 days, however, did not recover from anesthesia because of an overdose, extensive weight loss, or most probably because of both. The state of anesthesia/hypothermia induced by guanabenz was not reversed by naloxone, but was selectively reversed by yohimbine, tolazoline, and xanthines.

A group of four rats were administered i.p. guanabenz (12 mg/kg) at an ambient temperature of 21.3 °C. Their colonic, intraperitoneal, hepatic, and renal temperatures were compared with the vehicle-treated rats housed at a room temperature of 21.5 °C. The core temperature was measured at 5-min intervals, and that of the vital organs at 15 and 25 min post injection.

Stabilized at 25 min after guanabenz injection, the mean intraperitoneal temperature of 31.5 °C and that of the liver and kidneys (33.5 °C), respectively, were 9.5 °C

[a]This work was supported by Edmund A. Guggenheim, and Murray and Leonie Guggenheim Clinical Research Endowment Funds.

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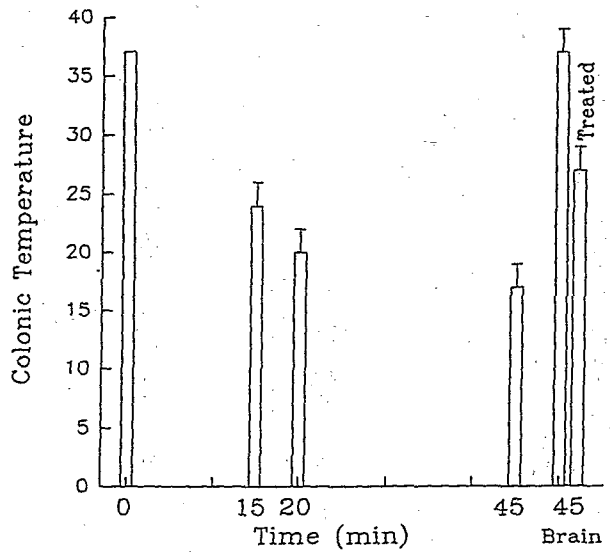

FIGURE 1. Guanabenz-induced hypothermia. Guanabenz (12 mg/kg) was administered i.p. to eight Sprague-Dawley rats. Immediately after injection of guanabenz or the vehicle (5% aqueous dextrose), the rats were placed in a temperature controlled room (4–5 °C). No change occurred in colonic and brain temperatures of the control rats. The brain temperature of guanabenz-treated rats, however, dropped by 10 °C (from 37 to 27 °C), and the colonic temperature dropped by 20 °C from 37 to 17 °C. Note that the onset of hypothermia is very rapid; the major drop in core temperature occurs within 15–20 min.

and 11.5 °C higher than the comparable mean colonic temperature of 22.5 °C for vehicle controls (TABLE 1).

Previous studies by Franz and co-workers[3,4] have shown that clonidine, an α2-adrenoceptor agonist, depresses transmission through sympathetic preganglionic neurons in the spinal cord, at least in part by reducing neuronal levels of cyclic AMP.

The state of anesthesia can be reversed by aminophyline, a cyclic-AMP phosphodiesterase inhibitor. Any agent that crosses the blood-brain barrier and increases cyclic-AMP levels, such as xanthines and β-adrenoceptor agonists, can reverse the state of anesthesia, but not that of hypothermia.

TABLE 1. Temperature Alterations after Treatment with Guanabenz[a]

Drug	Time (min)	Core	Intraperitoneal	Abdominal Cavity	Liver	Kidney
Guanabenz	15	22	31.5	31.5	33.5	33.5
	25	22.5	31.5	31.5	34.5	33.5
	40	22.6				
Vehicle (control)	15	35.5	37.0	37.8	38.2	38.2
	25	35.8	36.4	37.3	37.8	38.2
	40	35.6				

[a]Mean core temperature before injection was 35.5 ± 0.1 °C; ambient temperature, 21 °C.

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The mechanism of action of α2-adrenoceptor agonists is believed to be stimulation of α2-adrenoceptors in the central nervous system. Stimulation of the receptors in the vasomotor center and the nucleus tractus solitarii decreases the sympathetic nerve impulses to the peripheral organs, such as the heart and blood vessels, with consequent reduction of peripheral vascular resistance and hypotension. Thus, the induced state of anesthesia and deep hypothermia mimics hibernation and is compatible with life; if an adequate nutritional balance is maintained, a mammal can be kept in a hibernation-like state for a long period of time without any untoward effect.

ACKNOWLEDGMENTS

This paper is dedicated to Jude Sleis for her years of impeccable service. Her untimely departure leaves a great void. The support and help of my colleagues, Drs. Abel Lajtha, Henry Sershen, and Audrey Hashim, are gratefully acknowledged.

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